

Adverse Event	amlodipine		Placebo	
	M=% (N=1218)	F=% (N=512)	M=% (N=914)	F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in  $\leq 1\%$  but  $>0.1\%$  of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease. **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps, myalgia. **Psychiatric:** sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** dyspnea, epistaxis. **Skin and Appendages:** angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular. **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leukopenia, purpura, thrombocytopenia. The following events occurred in  $\leq 0.1\%$  of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina. Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine. Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. **The Atorvastatin Component of CADUET:** Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients,  $<2\%$  of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain. Clinical Adverse Experiences: Adverse experiences reported in  $\geq 2\%$  of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 3.

Table 3. Adverse Events in Placebo-Controlled Studies (% of Patients)

Body System/ Adverse Event	atorvastatin				
	Placebo N=270	10 mg N=863	20 mg N=36	40 mg N=79	80 mg N=94
<b>BODY AS A WHOLE</b>					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
<b>DIGESTIVE SYSTEM</b>					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
<b>RESPIRATORY SYSTEM</b>					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
<b>SKIN AND APPENDAGES</b>					
Rash	0.7	3.9	2.8	3.8	1.1
<b>MUSCULOSKELETAL SYSTEM</b>					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

**Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT):** In ASCOT involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up. The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in  $\geq 2\%$  of patients and the events in plain type occurred in  $<2\%$  of patients. **Body as a Whole:** Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. **Respiratory System:** Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis. **Nervous System:** Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia. **Musculoskeletal System:** Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. **Urogenital System:** Urinary tract infection, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Echinomysis, anemia, lymphadenopathy, thrombocytopenia, petechia. **Postintroduction Reports with Atorvastatin:** Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis. **Pediatric Patients (ages 10-17 years):** In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **PRECAUTIONS, Pediatric Use**).

**OVERDOSAGE:** There is no information on overdosage with CADUET in humans. **Information on Amlodipine:** Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum recommended clinical dose on a mg/m<sup>2</sup> basis) caused a marked peripheral vasodilation and hypotension. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. **Information on Atorvastatin:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

\*Based on patient weight of 50 kg.

\*\*These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

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Dublin, Ireland

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Division of Pfizer Inc., NY, NY 10017

Rev. 1 October 2004

## DRUGS, PREGNANCY, AND LACTATION

### Hair Testing and Maternal Drug Exposure

A recently published study on recreational drug use during pregnancy and the possible link to fetal gastroschisis highlights an increasingly important area of research: hair testing as a biomarker for pregnancy exposure to recreational drugs or drugs of abuse. Our laboratory is one of several sites in North America with expertise in measuring these substances in hair, an area many physicians may not be aware of.

Clearly, it can be difficult to determine the types of chemicals or drugs a fetus may have been exposed to by relying on what a woman says she took during pregnancy. The area of forensic science has provided us with a great deal of help in this area.

Forensic scientists have known for some time that drugs taken by an individual are grown into the hair, and do not go away. The first use of this technology was to detect long-term exposure to heavy metals. Over the last 15-20 years, more drugs of abuse have been determined to grow into adult hair, including cocaine, heroin, marijuana, LSD, amphetamine, and methamphetamine. In 1988, we determined that the same is true for the baby. Because the hair present at birth grows during the last 3 months of gestation, an analysis of a baby's hair can provide information on possible drug exposure during that time. We have now shown this is true for almost every drug of abuse, as well as nicotine.

With babies, the same substances can also be measured in meconium, and exposure can be traced to as early as 14 weeks' gestation, when meconium begins to form. Hair and meconium testing have become quite routine in certain settings in North America, with the predominant use among child protection agencies or children's aid societies. This testing is also used for research and clinical purposes and by neonatologists and other health care professionals who have a medical reason to test, often in the context of diagnosing issues in the child, and when maternal consent is provided. For such studies to be conducted, the guardian's consent is needed; sensitive attitudes and high ethical standards need to be practiced.

It's possible to use meconium analysis to test for excessive maternal alcohol intake by measuring fatty acid ethyl esters, conjugates of alcohol with fatty acids, which stay in the meconium of the baby. Recent work from investigators in Berlin determined that fatty acid ethyl esters can also be measured in the hair of the parents. Animal studies indicate they can be measured in a baby's hair, which is being investigated in human studies that are underway.

Analyzing hair samples provides an opportunity to look, not just at one sample of urine or blood that represents the last day or so of exposure but, rather, long-term exposure. At our laboratory, we use hair testing to determine when exposure

occurred, which eliminates the uncertainties when this information is obtained from the individual.

Last year we published a review (Clin. Biochemistry 2004;37:429-38) that discussed hair and meconium testing to confirm the prenatal use of alcohol and tobacco. It is important for clinicians to recognize that positive neonatal or meconium tests for drugs of abuse are strong evidence for maternal addiction, as these drugs have been used long after the mother knew she had conceived.

In a study conducted at the Motherisk laboratory published in 2003 (Arch. Dis. Child. Fetal Neonatal Ed. 2003;88:F98-F100), we found that meconium was somewhat more sensitive than hair samples of newborns for detecting cocaine and cannabis, and found a significant correlation between hair and meconium levels of cocaine, cannabis, and opiates. We concluded that both methods were useful biologic markers of illicit drug exposure in utero and also useful in suspicious cases where the neonatal urine test is negative.

In the recent gastroschisis study, investigators used maternal hair analysis from samples taken between 14 and 33 weeks' gestation in 22 pregnant women with a fetus diagnosed with the disorder and in 25 pregnant women with a normal fetus (BJOG 2005;112:1022-5).

In 10 of the 22 cases of babies with gastroschisis, there was evidence on enzyme-linked immunosorbent assay (ELISA) that the mother had taken a recreational drug during the periconceptional period and in the first trimester. But when they checked these results against those obtained from gas chromatography with mass spectrometry (GCMS), which is most specific, four cases (three of cocaine use and one of methamphetamine use) were confirmed.

While the study is small and therefore cannot establish an association, it marks the first time that "objective measurements of maternal intake of recreational drug compounds at these critical periods of development for the fetus have been carried out," as the researchers noted. This effort should be welcomed. Clearly, hair testing can be a very powerful tool in these studies and in individual cases to help determine whether a woman is using drugs.

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